Diabetes and the Heart

van den Hurk, K.

2011

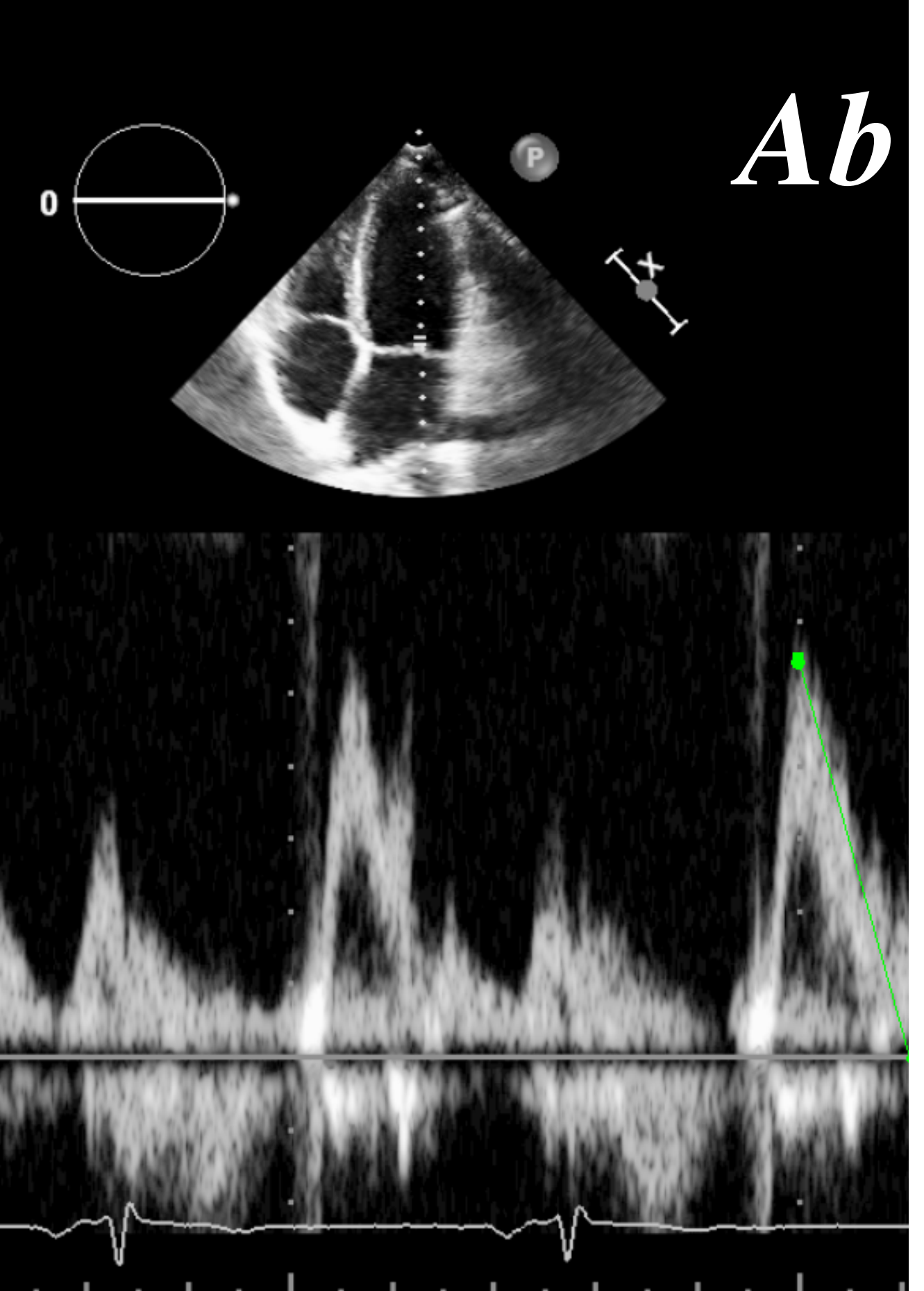
document version
Publisher's PDF, also known as Version of record

CHAPTER 5

Slightly elevated B-type Natriuretic Peptide levels in a non-heart failure range indicate a worse Left Ventricular Diastolic Function in individuals with, as compared to individuals without, Type 2 Diabetes: The Hoorn Study

K. van den Hurk
M. Alssema
O. Kamp
R.M. Henry
C.D.A. Stehouwer
M. Diamant
F. Boomsma
R.J. Heine
G. Nijpels
W.J. Paulus
J.M. Dekker

Eur J Heart Fail, 2010; 12(9):958-65


Ab
0
P

stract

Aims Higher plasma B-type natriuretic peptide (BNP) in a non-heart failure range predicts heart failure and cardiovascular disease (CVD) mortality in the general population. Heart failure is highly prevalent in type 2 diabetes, but associations of BNP to left ventricular (LV) mass and function in individuals with a different glucose status have not been compared. We therefore aimed to explore (1) the association of BNP levels in a non-heart failure range with structural and functional markers of LV function, and (2) possible effect modification by glucose tolerance categories.

Methods Linear regression analyses were performed to investigate associations of BNP with 2D echocardiographic measures of LV mass index, LV systolic function, and markers of LV diastolic function in a population-based study of men and women with normal glucose metabolism (n=197), impaired glucose metabolism (n=128), or type 2 diabetes (n=204).

Results Patients were aged between 50-87 years, had BNP levels below 50 pmol/l and no LV wall motion abnormalities. BNP levels ranged from 0.4 to 46.1 pmol/l, the median was 4.2 pmol/l. Higher BNP was significantly associated with increased LV mass and deteriorated LV diastolic function, but not with LV systolic function. BNP was more strongly associated with LV diastolic function in type 2 diabetes compared to normal glucose metabolism and impaired glucose metabolism.

Conclusion **BNP was associated with LV mass and markers of LV diastolic function and the association of BNP with the latter appeared to be particularly strong in individuals with type 2 diabetes. This implies that the presence or absence of type 2 diabetes should be taken into account if BNP levels are used to assess CVD risk.**

Introduction

Plasma B-type Natriuretic Peptide (BNP) is a neurohormone primarily secreted from the cardiac ventricles which is used as an easily obtained and fast marker to exclude heart failure. Its circulating concentrations are elevated in response to increased volume and pressure in the left ventricle (LV). Because of a high negative predictive value (90%), BNP levels below 100 pg/ml (equivalent to 28 pmol/l) exclude heart failure in symptomatic patients. The positive predictive value for BNP levels of 100 pg/ml and 200 pg/ml (equivalent to 57 pmol/l) respectively are 75% and 83%.[1] Therefore if BNP levels are above 200 pg/ml, additional non-invasive investigations are required for diagnosis of heart failure with a normal ejection fraction (HFNEF).

The Framingham Heart study showed a limited usefulness of BNP as a screening tool in the general population for LV hypertrophy or systolic dysfunction because of a low diagnostic performance.[2] However, in asymptomatic individuals, it has been shown that increased BNP levels below the threshold of 100 pg/ml, already indicate a higher risk of developing heart failure, atrial fibrillation, stroke, transient ischaemic attack, and death prospectively.[3] These slightly elevated BNP levels in a non-heart failure range thus cannot be used to diagnose heart disease, but may be important to indicate an increased risk.

It is well known that there is a high frequency of heart failure in men and women with type 2 diabetes. Also, the prognosis of heart failure is worse in diabetic patients compared to non-diabetic subjects.[4] Heart failure often develops gradually, after a period of compensating mechanisms to maintain stroke volume. These compensating mechanisms, LV dilation or hypertrophy with or without LV diastolic dysfunction, can be detected with echocardiography before symptoms occur. The Cardiovascular Health Study for instance showed that there is a linear relationship between LV mass index and incident heart failure.[5]

Other studies have shown that BNP is associated with LV abnormalities, cardiovascular disease (CVD) and mortality risk in type 2 diabetes patients.[6;7] These studies however did not compare associations of BNP with echocardiographic data in individuals with type 2 diabetes, or with impaired or normal glucose metabolism.

We hypothesized that BNP levels which are elevated but remain below the threshold for diagnosing heart failure, may indicate an increased LV mass and deteriorated LV function particularly in type 2 diabetes, indicating developing but still asymptomatic heart failure.[8] BNP levels may be of importance in detecting the risk of developing heart failure. Because of different exposures to other cardiovascular risk factors, implications may differ in individuals with normal glucose metabolism, impaired glucose metabolism, and type 2 diabetes. Thus, this study aimed to explore (1) the association of slightly elevated BNP levels in a non-heart failure range with structural and functional markers of LV function, and (2) possible effect modification by glucose tolerance categories.

Methods

For the present cross-sectional investigation, we used data from the Hoorn Study follow-up examination in the year 2000 and the Hoorn Screening Study, both of which were population-based.[9] Briefly, the Hoorn Study is a cohort study of glucose tolerance in the general population (n=2484), which started in 1989. In the year 2000, we invited all those who were diagnosed as having diabetes at the previous follow-up examination in the year 1996 (n=176), and random samples of individuals with normal (n=705) and impaired (n=193) glucose metabolism. Of the 1074 individuals invited, 648 (60%) agreed to participate. In addition, we invited 217 individuals with type 2 diabetes from the Hoorn Screening Study, a population-based targeted type 2 diabetes screening study in the year 2000, of whom 188 (87%) participated.[9]

Individuals who had BNP levels above 100 pmol/l or for whom data on BNP, LV mass, and/or LV function were missing were excluded from the analyses. To maintain the reliability of LV function data and to be sure to investigate associations independent of other cardiac disease, individuals with ischaemic heart disease (wall motion abnormalities (WMA) observed on echocardiography), with a heart rate > 90 bpm, or with atrial fibrillation were excluded. The study complied with the Declaration of Helsinki, the local ethics committee approved the study and written informed consent was obtained from all participants.

Plasma BNP was determined in spare frozen EDTA samples, which had been stored at –80°C for 4 years. BNP was determined in pmol/l (equivalent to 3.5 pg/ml) using an immunoradiometric assay kit (Shionoria, Osaka, Japan). Inter- and intra-assay variability coefficients were in the relevant range of <10%.[10]

A single ultrasound research technician, blinded to the participants' clinical or glucose tolerance status, obtained an LV echocardiogram according to a standardized protocol, with the use of an ultrasound scanner (HP SONOS 5500; 2-4 MHz transducer, Andover, Massachusetts, USA). 2-Dimensional and M-mode recordings were performed in parasternal long- and short-axis views, and apical four- and two-chamber views. All recordings were digitally stored and analyzed off-line by the ultrasound research technician. Each echocardiogram was subsequently inspected by a senior cardiologist, blinded to the participants' clinical and glucose status, to monitor the quality of the measurements and to check for LV wall motion abnormalities (WMA) and moderate or severe mitral valve insufficiency. LV mass and function were determined as follows:

(1) LV mass was calculated and indexed by height$^{2.7}$, resulting in LV mass index in grams/m$^{2.7.5}$.

(2) To account for an increase of LV mass index due to compensation of LV dilation, we used body surface area indexed LV mass divided by the LV end diastolic volume index (LV mass index / LV volume index) as a second measure of LV mass.[11]

(3) To assess LV systolic function, LV systolic and diastolic areas (A) and longest lengths (L) were measured from the apical four chamber view to determine the LV ejection fraction with the formula: LV ejection fraction (ml) = (Volume (V)$_{dias}$ - V$_{sys}$)/ V$_{dias}$, where V(ml) = $(8 \cdot A^2)/(3 \cdot \pi \cdot L)$.[12]

(4) One marker of LV diastolic function was left atrial (LA) volume index (ml/m^2): LA volume / body surface area (BSA).[13]

(5) A second marker of LV diastolic function was the product of LA volume and LV mass index (LAV*LVMI).[14]

Unfortunately no tissue Doppler measurements were available to grade LV diastolic dysfunction, however LA volume index was shown to be closely correlated to the severity of LV diastolic dysfunction.[13] LAV*LVMI has been shown to provide a better discrimination between HFNEF and asymptomatic LV hypertrophy than LA volume index or grades of LV diastolic dysfunction.[14]

All participants, except those with previously diagnosed diabetes (n=44), underwent a standard oral glucose tolerance test and were classified as either normal glucose metabolism, impaired glucose metabolism (an impaired fasting glucose and/or an impaired glucose tolerance), or type 2 diabetes according to the 2006 World Health Organisation criteria.[15] The simplified Modification of Diet in Renal Disease (MDRD) equation was used to estimate the glomerular filtration rate (eGFR, ml/min), with serum creatinine values recalculated into values standardized to reference methods.[16] Health status, medical history, medication use, and smoking habits were assessed by a questionnaire.[9] BMI, waist-hip ratio, blood pressure, prior CVD, serum total and HDL cholesterol, serum triglycerides, insulin, and HbA_{1c} were determined as described elsewhere.[9]

Statistical analysis

Descriptive statistics are presented as mean ± SD, or in case of a skewed distribution as median (interquartile range). The F test for analysis of variance in case of continuous variables or Chi^2 test in case of proportions, was performed to test for differences between tertiles of BNP and between men and women. In case of skewed distributions, tests were done on log-transformed data.

Linear regression was used to assess the association of plasma BNP levels with LV mass, LV systolic function and markers of LV diastolic function, for both sexes and categories of glucose tolerance status separately. Regression coefficients (ß) and 95% confidence intervals (CI) were reported and linearity of the regression models was judged based on residual histograms and P-P plots. To adjust for confounding, multivariable models including age and smoking were made. We investigated additional confounding or mediation by adding blood pressure, total and HDL cholesterol, HbA_{1c}, triglycerides, fasting plasma insulin and glucose levels, use of antihypertensive, lipid lowering, or type 2 diabetes medication, prior CVD, eGFR, mitral insufficiency and heart rate one by one to the age- and smoking-adjusted models. Variables that changed the ß's more than 10% were included in the final model, Model 3.

The influence of glucose status on the associations of BNP with LV mass and function was investigated based on the reported ß's for each group. ß's of 2 groups were considered significantly different if they were not present in each others CI's. The influence of sex on the associations of BNP with LV mass and function was tested equally, comparing men to women for the total population, and for normal glucose metabolism, impaired glucose metabolism, and type 2 diabetes separately. P values below 0.05 were considered statistically significant. Statistical analyses were performed with SPSS for Windows (version 14.0, SPSS Inc., Chicago, IL).

Additional analyses were done to investigate whether exclusion of individuals with presence of prior CVD, use of medication (lipid lowering, antihypertensive or glucose lowering or all together), known diabetes, screened (or newly diagnosed) type 2 diabetes, high pulse pressure (≥80 mmHg), high lipid levels (total cholesterol ≥6.5 mmol/l and/or triglycerides ≥2 mmol/l), high insulin levels (≥100 pmol/l), low heart rate (≤60 bpm), mitral insufficiency, WMA or low eGFR (MDRD ≤60 ml/min/1.73m^2) influenced the associations. We therefore repeated all regression analyses with exclusion of these individuals (one factor at a time) and verified whether this changed the results.

Results

BNP levels were obtained for 671 individuals, 3 (0.4%) of them were excluded because of BNP levels >100 pmol/l, and 78 (11.6%) because of missing echocardiographic data, which was mostly due to high BMI.17 Seven (1.0%) more were excluded for missing data on glucose status, 3 (0.4%) because of a heart rate >90 bpm, 12 (1.8%) because of atrial fibrillation, and 39 (5.8%) because they had WMA which modified the association between BNP and LV systolic function. The final study population therefore consisted of 197 individuals with normal glucose metabolism, 128 with impaired glucose metabolism, and 204 with type 2 diabetes. BNP ranged from 0.4 to 46.1 pmol/l, and showed a skewed distribution. Median BNP was 4.2 (interquartile range 2.0 and 8.0) pmol/l.

Surprisingly, type 2 diabetes appeared to be less prevalent in the highest BNP tertile and individuals in this category had lower insulin (men only), triglycerides and cholesterol (women only) levels, compared to the lowest tertile (Table 5.1). Age, blood pressure, and LV mass increased and LV diastolic function worsened with increasing BNP levels. LV systolic function was similar for all tertiles. Women had higher BNP levels, were older and had higher blood pressure, antihypertensive medication use, heart rate, cholesterol and better LV systolic function, and lower waist-hip ratio, LV mass index and eGFR compared to men.

Figures 5.1-5.3 show the values of LV mass index, LA volume index and LAV*LVMI per individual with the fitted regression curves for individuals with normal glucose metabolism, impaired glucose metabolism and type 2 diabetes. In men with type 2 diabetes and women with impaired glucose metabolism or type 2 diabetes, a 10 pmol/l increase of BNP was significantly associated with, respectively, a 14.2, 8.7, and 10.2 g/m^2 higher LV mass index after adjustment for age, smoking, the use of antihypertensive medication, waist-hip ratio, systolic blood pressure, and mitral insufficiency (Table 5.2, Model 3). Associations of BNP with LV mass index / LV volume index and with LV systolic function were similar for all subgroups, therefore we only reported ß's for the total population, with additional adjustment for sex and glucose status (Table 5.3). BNP was significantly associated with LV mass index / LV volume index; ß=0.09 (0.02-0.16) per 10 pmol/l increase of BNP, but not with LV systolic function. BNP was significantly associated with LA volume index in all subgroups of sex and glucose status, with ß's ranging from 2.4 g/m^2 (in women with normal glucose metabolism) to 9.3 g/m^2 per 10 pmol/l increase of BNP. The association was significantly stronger for men with type 2 diabetes or normal glucose metabolism as compared to men with impaired glucose metabolism and for women with type 2 diabetes as compared to women with normal glucose metabolism or impaired glucose metabolism. A 10 pmol/l higher BNP was also significantly associated with a higher LAV*LVMI in all subgroups, varying from 233 ml*g/m$^{2.7}$. in women with normal glucose metabolism to 1460 ml*g/m$^{2.7}$. in men with type 2 diabetes. In both men and women, the association between BNP and this second measure of LV diastolic function was significantly stronger in individuals with type 2 diabetes as compared to those with normal glucose metabolism or impaired glucose metabolism.

There appeared to be a significant association between BNP and LV systolic function in the total study population. This association was in fact only present in individuals with WMA and not in those without, therefore we excluded individuals with WMA (data not shown). Exclusion of the other groups of individuals as described in our methods did not alter any of the fully adjusted associations.

Table 5.1: Characteristics of the study population according to sex and tertiles of BNP

	men			Women		
N	BNP < 2.8	BNP 2.8-6.7	BNP > 6.7	BNP < 2.8	BNP 2.8-6.7	BNP > 6.7
	98	81	68	80	104	98
BNP (pmol/l) *	1.5 (1.0-2.0)	3.9 (3.2-5.5) †	11.6 (8.8-16.3) ‡§	1.4 (1.1-2.0)	4.7 (3.6-5.7) †	9.9 (8.0-15.4) ‡§
% smoker	12.2	24.7 †	11.8 ‡	12.7	14.6	9.2
% impaired glucose metabolism	23.5	23.5	25.0	20.0	25.0	27.6
% type 2 diabetes	41.8	42.0	35.3	48.8	36.5	28.6 §
Age (yrs) *	66 ± 6	68 ± 7	71 ± 8 ‡§	66 ± 7	69 ± 6 †	71 ± 6 §
Body mass index (kg/m^2)	27.3 ± 3.3	27.0 ± 3.4	27.2 ± 3.3	28.0 ± 4.3	27.5 ± 3.7	27.0 ± 4.1
Waist-hip ratio *	0.98 ± 0.07	0.99 ± 0.07	0.98 ± 0.07	0.89 ± 0.08	0.88 ± 0.06	0.86 ± 0.07 §
Heart rate (bpm) *	63 ± 9	62 ± 8	57 ± 9 ‡§	65 ± 9	65 ± 10	61 ± 9 ‡§
Systolic pressure (mmHg) *	137 ± 13	141 ± 17	144 ± 19 §	140 ± 20	145 ± 20	151 ± 24 §
Diastolic pressure (mmHg) *	79 ± 8	78 ± 9	78 ± 9	75 ± 9	77 ± 9	77 ± 10
% antihypertensive medication *	18.4	28.4	47.1 ‡§	30.4	38.5	48.0 §
% lipid lowering medication	11.2	16.0	16.2	12.7	12.5	14.3
% type 2 diabetes medication	5.1	7.4	10.3	11.4	7.7	3.1 §
Fasting glucose (mmol/l)	6.1 (5.6-7.0)	6.2 (5.7-6.9)	6.1 (5.4-6.9)	6.4 (5.6-7.2)	6.1 (5.5-6.9)	5.8 (5.3-6.4) §
Post-load glucose (mmol/l)	6.9 (5.0-8.5)	6.3 (5.4-8.4)	6.1 (5.2-8.1)	6.3 (5.3-7.8)	7.0 (5.6-9.0)	7.0 (5.4-8.7)
HbA_{1c} (%)	5.9 (5.5-6.4)	5.9 (5.5-6.5)	5.8 (5.5-6.3)	6.1 (5.7-6.4)	6.0 (5.6-6.4)	5.8 (5.5-6.1) §
Insulin (pmol/l)	70 (46-100)	60 (45-84)	50 (37-72) ‡§	68 (43-100)	61 (50-86)	55 (37-78)
Total cholesterol (mmol/l) *	5.5 ± 1.0	5.3 ± 0.9	5.2 ± 0.9	6.3 ± 1.1	6.1 ± 1.0	5.9 ± 0.9 §
HDL cholesterol (mmol/l) *	1.2 ± 0.3	1.3 ± 0.4	1.3 ± 0.3	1.5 ± 0.4	1.5 ± 0.4	1.7 ± 0.4 ‡§
Triglycerides (mmol/l)	1.5 (1.1-2.2)	1.3 (1.0-1.7) †	1.2 (0.9-1.4) §	1.4 (1.0-2.0)	1.4 (1.0-1.9)	1.2 (0.9-1.5) ‡§
eGFR (MDRD, ml/min/1.73m^2) *	83 ± 18	83 ± 17	80 ± 17	82 ± 14	80 ± 17	80 ± 18
% prior CVD	33.3	44.2	53.7 §	46.1	45.0	51.0
% mitral insufficiency (moderate-severe)	0.0	2.5	5.9 §	0.0	1.0	5.1
LV mass index (g/m$^{2.7}$) *	37 (32-44)	37 (31-44)	45 (33-57) ‡§	39 (32-44)	41 (34-48)	43 (31-55)
LV mass index / LV volume index	1.6 (1.3-2.0)	1.6 (1.4-2.0)	1.8 (1.4-2.3) §	1.7 (1.4-2.0)	1.7 (1.5-2.1)	1.7 (1.4-2.3)
LV ejection fraction (%) *	60 ± 7	59 ± 8	61 ± 8	63 ± 7	64 ± 7	63 ± 7
LA volume index (ml/m^2)	21 (18-24)	21 (19-26)	28 (23-35) ‡§	21 (18-24)	22 (19-26)	26 (21-32) ‡§
LA volume*LV mass index (ml*g/m$^{2.7}$)	1513 (1154-2018)	1669 (1258-2127)	2576 (1655-3620) ‡§	1450 (1121-1888)	1609 (1221-2098))	2035 (1335-2771) ‡§

Data are reported as mean ± SD or median (interquartile range). BNP = B-type natriuretic peptide, HbA1c = Haemoglobin type A1c, HDL = high density lipoprotein, eGFR = estimated glomerular filtration rate , LV = left ventricular, LA = left atrial. *p<0.05 for men vs women, † p<0.05 for tertile 1 vs 2, ‡ p<0.05 for tertile 2 vs 3, § p<0.05 for tertile 1 vs 3.

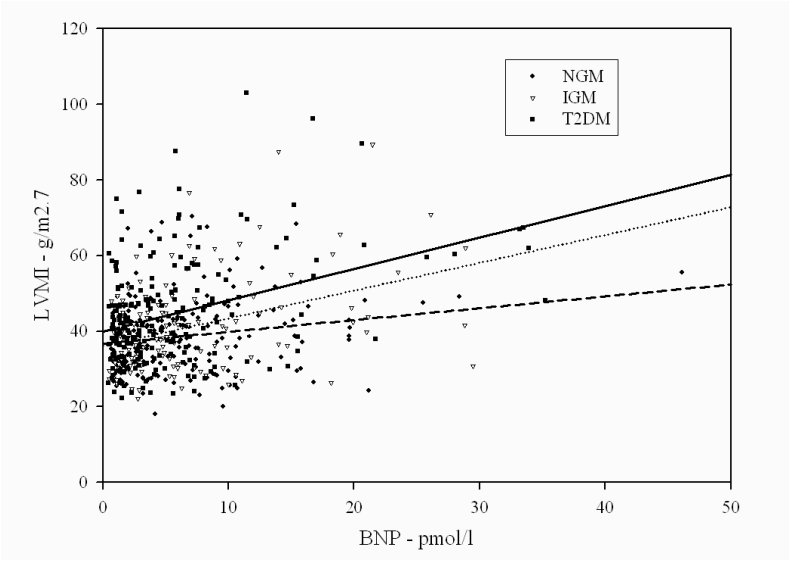


Figure 5.1: Scatter plot with fitted regression curves (unadjusted) of BNP and LV mass index (LVMI, $g/m^{2.7}$) for individuals with normal glucose metabolism (NGM , dashed line), impaired glucose metabolism (IGM, dotted line) and type 2 diabetes (T2DM, solid line).

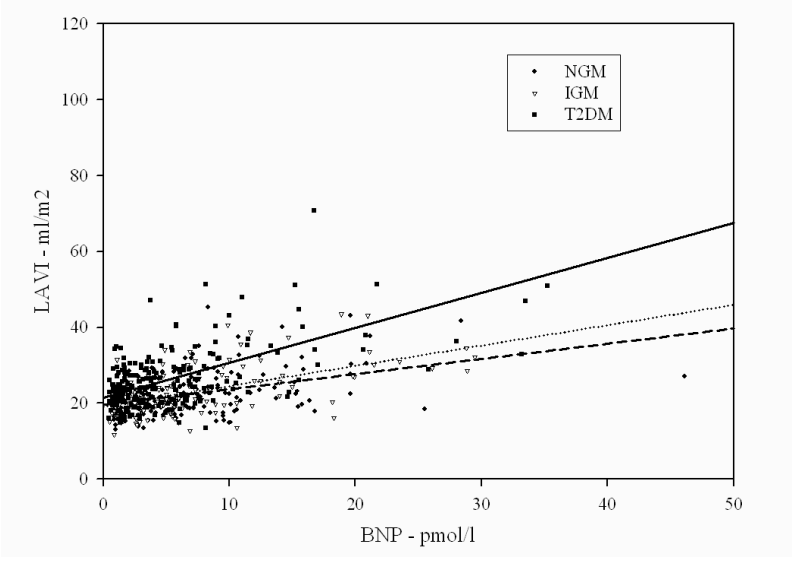


Figure 5.2: Scatter plot with fitted regression curves (unadjusted) of BNP and LA volume index (LAVI, ml/m^2) for individuals with normal glucose metabolism (NGM , dashed line), impaired glucose metabolism (IGM, dotted line) and type 2 diabetes (T2DM, solid line).

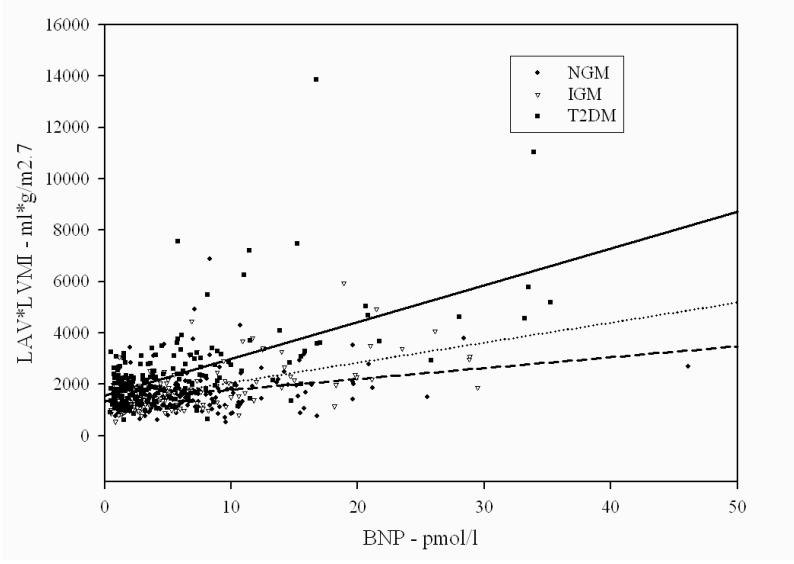


Figure 5.3: Scatter plot with fitted regression curves (unadjusted) of BNP and LA volume * LV mass index (LAV*LVMI, ml*g/$m^{2.7}$) for individuals with normal glucose metabolism (NGM , dashed line), impaired glucose metabolism (IGM, dotted line) and type 2 diabetes (T2DM, solid line).

Table 5.3: Regression coefficients per 10 pmol/l increase of BNP for LV mass / LV volume index and LV systolic function

Model	Total population, n=529
BNP (median & interquartile range)	4.2 (2.0-8.0)
LV mass index / LV volume index	
Crude model	0.17* (0.10 – 0.24)
Model 2	0.14* (0.07 – 0.21)
Model 3	0.09* (0.02 – 0.16)
LV ejection fraction (%)	
Crude model	-0.21 (-1.24 – 0.81)
Model 2	-0.75 (-1.77 – 0.27))
Model 3	-0.50 (-1.57 – 0.57)

Model 2: adjusted for age, smoking, sex, and glucose status, Model 3: Model 2 + use of antihypertensive medications, systolic blood pressure, waist-hip ratio, and mitral insufficiency. BNP=B-type Natriuretic Peptide, LV=left ventricle. * p<0.05

Table 5.2: Regression coefficients per 10 pmol/l increase of BNP for LV mass and LV diastolic function, stratified for sex and glucose status

		men			Women	
Model	NGM n=89	IGM n=59	T2DM n=99	NGM n=108	IGM n=69	T2DM n=105
	3.3 (1.9-7.9)	3.5 (1.6-7.8)	3.3 (1.6-6.8)	5.6 (2.8-9.0)	5.5 (2.9-9.7)	4.0 (1.4-7.3)
BNP (median & interquartile range)						
LV mass index (g/m$^{2.7}$)						
Crude model	3.3 (-0.7 - 7.3)	5.8* (0.7 - 10.9)	9.8* (5.1 - 14.4)§	3.3* (0.4 - 6.1)	6.7* (2.4 - 11.1)	6.9* (3.1 - 10.7)
Model 2	3.1 (-1.5 - 7.7)	5.8* (0.3 - 11.2)	8.9* (4.3 - 13.4)§	2.4 (-0.3 - 5.2)	6.7* (2.5 - 10.9)	6.4* (2.3 - 10.5)
Model 3	3.4 (-1.2 - 8.0)	5.2 (-0.3 - 10.7)	6.4* (2.3 - 10.6)	1.0 (-1.6 - 3.7)	4.5* (0.2 - 8.7)	4.9* (0.4 - 9.3)
LA volume index (ml/m^2)						
Crude model	6.7* (4.6-8.8)	6.0* (3.7-8.4)	7.6* (5.2-10.1)	2.5* (1.2-3.9)†	5.1* (3.1-7.1)‡	10.6* (8.3-13.0)†§||
Model 2	7.4* (4.9-9.8)	5.6* (3.1-8.2)	7.6* (5.1-10.1)	2.3* (1.0-3.7)†	4.9* (2.9-6.9)‡	11.0* (8.4-13.5)†§||
Model 3	7.4* (4.9-9.9)	4.5* (1.7-7.3)‡	8.7* (6.1-11.3)||	2.4* (1.0-3.8)†	4.0* (1.9-6.1)	9.3* (6.8-11.8)§||
LA volume*LV mass index (ml*g/m$^{2.7}$)						
Crude model	682* (324-1041)	809* (462-1157)	1470* (973-1966)§||	327* (167-488)	714* (441-986)‡	1424* (1136-1712)§||
Model 2	772* (360-1183)	802* (434-1170)	1439* (937-1940)§||	288* (130-445)†	696* (423-970)‡	1478* (1167-1789)§||
Model 3	810* (399-1221)	661* (293-1028)	1460* (951-1969)§||	233* (74-391)†	492* (221-763)	1235* (936-1533)§||

Model 2: adjusted for age and smoking, Model 3: Model 2 + use of antihypertensive medications, systolic blood pressure, waist-hip ratio, and mitral insufficiency. BNP=B-type Natriuretic Peptide, LV=left ventricle, LA=left atrium, NGM=normal glucose metabolism, IGM=impaired glucose metabolism, T2DM=type 2 diabetes mellitus. * $p<0.05$, † $p<0.05$ for women vs men, ‡ $p<0.05$ for IGM vs NGM, § $p<0.05$ for T2DM vs NGM, || $p<0.05$ for T2DM vs IGM

Discussion

The present population-based study has two main conclusions. First, this study showed that increased BNP levels in a non-heart failure range were significantly associated with increased LV mass and deteriorated LV diastolic function in both men and women, independently of traditional cardiovascular risk factors. Second, it was clearly shown that the association of BNP with markers of LV diastolic function was stronger in individuals with type 2 diabetes as compared to those with normal glucose metabolism, despite the similar range of BNP levels in the different groups of glucose status. In summary, our study confirms previous findings that BNP levels in a non-heart failure range already indicate CVD risk and furthermore it implies that potential risk estimations based on BNP levels should take the presence or absence of type 2 diabetes into account, since this amplifies the associations.

BNP as a marker for risk

This population-based study extends previous findings that elevated BNP levels in a non-heart failure range are associated with developing LV abnormalities, most of which have focused on different populations than the present study, for example (clinically) selected populations,[7] a random sample of the general population,[18] or type 2 diabetes patients only.[7]

Our results support the idea that the higher CVD and mortality risk associated with higher BNP levels in a non-heart failure range result from a deteriorated LV diastolic function and LV hypertrophy, but not LV systolic function. LV diastolic dysfunction and LV hypertrophy may precede LV systolic dysfunction, symptomatic or asymptomatic HFNEF, or mortality.[8;19] Higher BNP levels in a non-heart failure range can thus give an early indication of CVD and mortality risk.

BNP as a marker for risk in type 2 diabetes mellitus

An important finding in this study is that BNP levels were associated more strongly with markers of LV diastolic function in individuals with type 2 diabetes as compared to those with normal glucose metabolism or impaired glucose metabolism. In other words, similar BNP levels indicate a worse LV diastolic function if an individual has type 2 diabetes. Also, the influence of type 2 diabetes on the association between BNP and markers of LV diastolic function is probably underestimated because of non-attendance due to morbidity and mortality in individuals with high glucose levels and deteriorated LV function, and the fact that the ability to obtain full echocardiographic data is hindered by obesity. In men only we found BNP less strongly associated with LA volume index in impaired glucose metabolism as compared to normal glucose metabolism. Since this association was not consistently present in other analyses, this may be a chance finding.

To our knowledge, this is the first study to compare how BNP levels relate to LV mass and function in individuals with normal glucose metabolism, impaired glucose metabolism and type 2 diabetes. Magnusson et al. found higher BNP levels in type 2 diabetes patients compared to healthy controls, but these results were not confirmed by echocardiographic data.[20] Another study found correlations between BNP and LV diastolic function in type 2 diabetes, hypertensive and healthy subjects, but the small number of participants were not directly compared to each other.[21]

Higher glucose levels seem to have a more stiffening effect on the myocardium, leading to a deterioration of LV diastolic function. HFNEF is indeed highly prevalent in type 2 diabetes, especially in women, and has a prognosis equal to heart failure with a reduced ejection fraction.[19;22] It has recently been shown that even in a population without evidence of heart disease, glucose levels are associated with markers of LV diastolic function. The same study showed that type 2 diabetes is independently associated with the presence of LV diastolic dysfunction.[23] The stiffening effect of higher glucose levels was supported by the recent finding that cardiomyocyte resting tension was higher in type 2 diabetes patients with HFNEF than in non-type 2 diabetes subjects with HFNEF.[24] This is probably just partly reflected in BNP levels, resulting in increased BNP clearance in type 2 diabetes individuals.[25] This hypothesis might explain the augmented association between BNP and markers of LV diastolic function by type 2 diabetes.

Factors influencing BNP

BNP levels may degrade after storage at -80˚C, however Biosite Triage assay BNP testing after 1 year of storage did not show a significant decay for low (<100 pg/ml) BNP levels.[26] BNP levels are known to be influenced by age, gender, other cardiac diseases like myocardial infarction and valvular heart disease, and medication use.[27] Renal failure, which often occurs together with heart failure, gives rise to higher plasma BNP levels in 2 ways: an increased secretion through hypervolaemia, and a decreased urinary excretion.[28] Several studies have shown that obesity reduces the expression of natriuretic peptides, even in the presence of heart failure.[25] However, in our study we took renal function, BMI and waist-hip ratio, valvular disease and medication use into account through adjusted analyses and additional analyses with exclusion of high-risk individuals and can therefore conclude with reasonable confidence that the reported associations between BNP and markers of LV diastolic function were free from additional confounding and mediation. Our results therefore indicate that higher BNP levels in a non-heart failure range are probably a direct result of deteriorated LV diastolic function, probably through elevated pressures in the left ventricle and atrium.

Use of BNP levels in a non-heart failure range

An early diagnosis of heart failure would possibly facilitate treatment to improve the prognosis of type 2 diabetes patients at high risk of CVD mortality. Although no effective treatment of HFNEF has been developed yet, adherence to a healthy lifestyle has been shown to lower the risk of heart failure effectively,[29] and the effect of sildenafil on HFNEF is currently under study in a clinical trial (ClinicalTrials.gov Identifier: NCT00763867). BNP measurements could help in detecting these patients with or at high risk of developing HFNEF. This could for instance aid in deciding on prescription of sulfonylurea, which might increase heart failure risk.[30] The current study, however, indicates that interpretation of BNP levels should be done differently in type 2 diabetes patients as compared to individuals without type 2 diabetes.

Prospective studies would be necessary to determine whether high BNP levels also predict a deterioration in LV diastolic function or incident HFNEF in individuals with different glucose levels. Also, more insight is needed into whether treatment of high-risk individuals, based on BNP measurements, is beneficial to prevent or postpone heart failure and CVD mortality.

Limitations

One limitation of this study is that echocardiograms were checked but not re-analysed by a second person. Nonetheless, measurements were performed in threefold by a single technician, thus avoiding inter-observer variability. Another limitation is that no tissue Doppler measurements were available. However, we used markers of LV diastolic function which have been shown to be associated with (incident) heart failure and/or mortality.[5;13;14]

In conclusion, higher BNP levels in a non-heart failure range are indeed associated cross-sectionally with an increased LV mass and deteriorated markers of LV diastolic function, and the latter appears to be stronger in individuals with type 2 diabetes than with normal glucose metabolism. This finding supports the idea that higher BNP levels may indicate risk of CVD and mortality, furthermore it implies that the presence or absence of type 2 diabetes should be taken into account if BNP is used to estimate risk.

References

(1) Maisel AS, McCord J, Nowak RM, Hollander JE, Wu AH, Duc P et al. Bedside B-Type natriuretic peptide in the emergency diagnosis of heart failure with reduced or preserved ejection fraction. Results from the Breathing Not Properly Multinational Study. J Am Coll Cardiol 2003; 41(11):2010-2017.

(2) Vasan RS, Benjamin EJ, Larson MG, Leip EP, Wang TJ, Wilson PW et al. Plasma natriuretic peptides for community screening for left ventricular hypertrophy and systolic dysfunction: the Framingham heart study. JAMA 2002; 288(10):1252-1259.

(3) Wang TJ, Larson MG, Levy D, Benjamin EJ, Leip EP, Omland T et al. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. N Engl J Med 2004; 350(7):655-663.

(4) Dries DL, Sweitzer NK, Drazner MH, Stevenson LW, Gersh BJ. Prognostic impact of diabetes mellitus in patients with heart failure according to the etiology of left ventricular systolic dysfunction. J Am Coll Cardiol 2001; 38(2):421-428.

(5) de Simone G, Gottdiener JS, Chinali M, Maurer MS. Left ventricular mass predicts heart failure not related to previous myocardial infarction: the Cardiovascular Health Study. Eur Heart J 2008; 29(6):741-747.

(6) Bhalla MA, Chiang A, Epshteyn VA, Kazanegra R, Bhalla V, Clopton P et al. Prognostic role of B-type natriuretic peptide levels in patients with type 2 diabetes mellitus. J Am Coll Cardiol 2004; 44(5):1047-1052.

(7) Epshteyn V, Morrison K, Krishnaswamy P, Kazanegra R, Clopton P, Mudaliar S et al. Utility of B-type natriuretic peptide (BNP) as a screen for left ventricular dysfunction in patients with diabetes. Diabetes Care 2003; 26(7):2081-2087.

(8) Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur J Heart Fail 2008; 10(10):933-989.

(9) Henry RM, Kostense PJ, Spijkerman AM, Dekker JM, Nijpels G, Heine RJ et al. Arterial stiffness increases with deteriorating glucose tolerance status: the Hoorn Study. Circulation 2003; 107(16):2089-2095.

(10) Boomsma F, Deinum J, van den Meiracker AH. Relationship between natriuretic peptide concentrations in plasma and posture during blood sampling. Clin Chem 2001; 47(5):963-965.

(11) van Heerebeek L, Borbely A, Niessen HW, Bronzwaer JG, van der Velden J, Stienen GJ et al. Myocardial structure and function differ in systolic and diastolic heart failure. Circulation 2006; 113(16):1966-1973.

(12) Folland ED, Parisi AF, Moynihan PF, Jones DR, Feldman CL, Tow DE. Assessment of left ventricular ejection fraction and volumes by real-time, two-dimensional echocardiography. A comparison of cineangiographic and radionuclide techniques. Circulation 1979; 60(4):760-766.

(13) Pritchett AM, Mahoney DW, Jacobsen SJ, Rodeheffer RJ, Karon BL, Redfield MM. Diastolic dysfunction and left atrial volume: a population-based study. J Am Coll Cardiol 2005; 45(1):87-92.

(14) Melenovsky V, Borlaug BA, Rosen B, Hay I, Ferruci L, Morell CH et al. Cardiovascular features of heart failure with preserved ejection fraction versus nonfailing hypertensive left ventricular hypertrophy in the urban Baltimore community: the role of atrial remodeling/dysfunction. J Am Coll Cardiol 2007; 49(2):198-207.

(15) World Health Organisation, International Diabetes Federation. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia: report of a WHO/IDF consultation. 2006. Geneva, Switzerland, WHO Document Production Services.

(16) Levey AS, Coresh J, Greene T, Marsh J, Stevens LA, Kusek JW et al. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. Clin Chem 2007; 53(4):766-772.

(17) Henry RM, Ferreira I, Kostense PJ, Dekker JM, Nijpels G, Heine RJ et al. Type 2 diabetes is associated with impaired endothelium-dependent, flow-mediated dilation, but impaired glucose metabolism is not; The Hoorn Study. Atherosclerosis 2004; 174(1):49-56.

(18) Goetze JP, Mogelvang R, Maage L, Scharling H, Schnohr P, Sogaard P et al. Plasma pro-B-type natriuretic peptide in the general population: screening for left ventricular hypertrophy and systolic dysfunction. Eur Heart J 2006; 27(24):3004-3010.

(19) Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A et al. Outcome of heart failure with preserved ejection fraction in a population-based study. N Engl J Med 2006; 355(3):260-269.

(20) Magnusson M, Melander O, Israelsson B, Grubb A, Groop L, Jovinge S. Elevated plasma levels of Nt-proBNP in patients with type 2 diabetes without overt cardiovascular disease. Diabetes Care 2004; 27(8):1929-1935.

(21) Lim HS, Patel JV, Nadar S, Hughes EA, Lip GYH. Comparison of brain natriuretic peptide and left ventricular diastolic function determined by tissue Doppler in patients with diabetes mellitus, patients with hypertension without diabetes, and in healthy subjects. Am J Cardiol 2005; 95(7):905-908.

(22) Klapholz M, Maurer M, Lowe AM, Messineo F, Meisner JS, Mitchell J et al. Hospitalization for heart failure in the presence of a normal left ventricular ejection fraction: results of the New York Heart Failure Registry. J Am Coll Cardiol 2004; 43(8):1432-1438.

(23) Russo C, Jin Z, Homma S, Rundek T, Elkind MS, Sacco RL et al. Effect of diabetes and hypertension on left ventricular diastolic function in a high-risk population without evidence of heart disease. Eur J Heart Fail 2010; 12(5):454-461.

(24) van Heerebeek L, Hamdani N, Handoko ML, Falcao-Pires I, Musters RJ, Kupreishvili K et al. Diastolic stiffness of the failing diabetic heart: importance of fibrosis, advanced glycation end products, and myocyte resting tension. Circulation 2008; 117(1):43-51.

(25) Wang TJ, Larson MG, Levy D, Benjamin EJ, Leip EP, Wilson PWF et al. Impact of obesity on plasma natriuretic peptide levels. Circulation 2004; 109(5):594-600.

(26) Pereira M, Azevedo A, Severo M, Barros H. Long-term stability of endogenous B-type natriuretic peptide after storage at -20 degrees C or -80 degrees C. Clin Chem Lab Med 2008; 46(8):1171-1174.

(27) Daniels LB, Maisel AS. Natriuretic peptides. J Am Coll Cardiol 2007; 50(25):2357-2368.

(28) Linssen GC, Damman K, Hillege HL, Navis G, van Veldhuisen DJ, Voors AA. Urinary N-terminal prohormone brain natriuretic peptide excretion in patients with chronic heart failure. Circulation 2009; 120(1):35-41.

(29) Djousse L, Driver JA, Gaziano JM. Relation between modifiable lifestyle factors and lifetime risk of heart failure. JAMA 2009; 302(4):394-400.

(30) McAlister FA, Eurich DT, Majumdar SR, Johnson JA. The risk of heart failure in patients with type 2 diabetes treated with oral agent monotherapy. Eur J Heart Fail 2008; 10(7):703-708.